Dysregulation of cardiac endothelial lncRNA H19 in COVID19 patients induces endothelial dysfunction, which impairs cardiomyocyte function

R.P. Juni, P. Phelp, D. Bink, P. Espinoza-Gonzales, A. Van Bergen, D. Kuster, J. Van Der Velden, P. Krijnen, H. Niessen, R. Boon

Amsterdam UMC - Location VUmc, Amsterdam, The Netherlands
On behalf of COVID Biobank Study Group

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Background: COVID19 is accompanied by cardiac complications. Long non-coding RNAs (lncRNAs) have been implicated in the pathogenesis of cardiovascular diseases. However, their contribution to the cardiac manifestation of COVID19 is unknown.

Methods and results: We discovered that endothelial-enriched lncRNA H19 is downregulated in the heart of patients with COVID19 (∼2 fold, $p<0.01$). H19 was highly expressed in cardiac microvascular endothelial cells (CMEC) as compared to the other endothelial cell types (∼10 fold, $p<0.05$), suggesting its cardiac enrichment. H19 silencing in CMEC induced endothelial stress phenotype and a reduction in endothelial markers VE-cadherin and eNOS (∼1.5 fold, $p<0.01$), indicating its importance in endothelial physiology. Using the endothelial-cardiomyocyte coculture system we previously developed, we showed that H19 silencing in CMEC reduced cardiomyocyte (CM) relaxation and contraction (∼1.5 fold, $p<0.01$). Interestingly, exposure to plasma from COVID19 patients decreased endothelial H19 level and impaired endothelial enhancement of CM function. Mechanistically, reduced level of H19 increased endothelial IL6 expression (∼1.5 fold, $p<0.01$). Further, exposure of CMs to IL6 also impaired CM relaxation and contraction, suggesting that endothelial cells devoid of H19 release IL6 which represses CM function. Interestingly, we found increased IL6 levels in the heart of COVID19 patients (∼2 fold, $p<0.05$). Indeed, the impairment of endothelial enhancement of CM function upon H19 silencing in CMEC was restored in the presence of tocilizumab, an IL6 receptor antagonist (∼1.5 fold, $p<0.01$). Furthermore, the impairment of the endothelial control on CM function upon exposure to COVID19 plasma was mitigated when the patients were treated with tocilizumab (∼1.5 fold, $p<0.01$).

Conclusion: COVID19 reduces cardiac endothelial H19 level and induces impairment of endothelial enhancement of CM function via increased release of endothelial-derived IL6, the effect that can be rescued in the presence of IL6 receptor blocker tocilizumab.

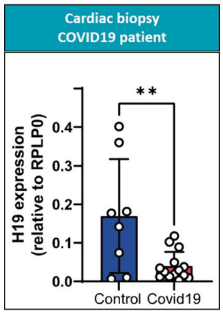

Figure 1

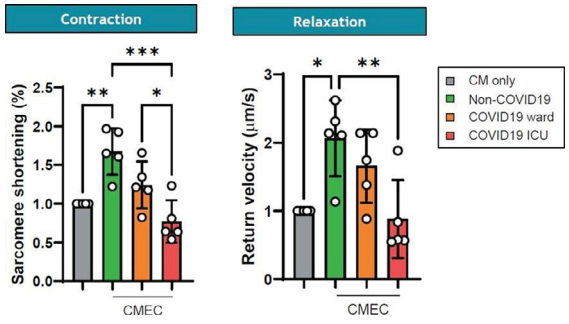

Figure 2